of 47,623

(FILE 'HOME' ENTERED AT 14:51:36 ON 25 JUL 2003)

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 14:51:45 ON 25 JUL 2003

L1 326 S (DYRBERG, T? OR DYRBERG T?)/AU,IN
L2 50 S (WORSAAE, A? OR WORSAAE A?)/AU,IN
L3 15 S L1 AND L2
L4 7 DUP REM L3 (8 DUPLICATES REMOVED)
L5 361 S L1 OR L2
L6 346 S L5 NOT L3
L7 234 S L6 AND INSULIN?
L8 0 S L7 AND B25
L9 1 S L6 AND (INSULIN?)(3A)(ANALOG?)

FILE 'STNGUIDE' ENTERED AT 14:54:23 ON 25 JUL 2003

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 14:57:43 ON 25 JUL 2003

L10 8 S (MANDIC, J? OR MANDIC J?)/AU,IN
L11 8 DUP REM L10 (0 DUPLICATES REMOVED)
L12 32 S (B25)(5A)(ASP?)
L13 17 DUP REM L12 (15 DUPLICATES REMOVED)
L14 11 S L13 AND INSULIN?

FILE 'STNGUIDE' ENTERED AT 15:06:45 ON 25 JUL 2003

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 15:08:15 ON 25 JUL 2003

FILE 'STNGUIDE' ENTERED AT 15:09:32 ON 25 JUL 2003

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 15:10:15 ON 25 JUL 2003

L14 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1990:491524 CAPLUS
DN 113:91524
TI Identification of residues in the **insulin** molecule important for binding to **insulin**-degrading enzyme
AU Affholter, Joseph A.; Cascieri, Margaret A.; Bayne, Marvin L.; Brange, Jens; Casaretto, Monika; Roth, Richard A.
CS Sch. Med., Stanford Univ., Stanford, CA, 94305, USA
SO Biochemistry (1990), 29(33), 7727-33
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English

=> d 5 ab,

L14 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2003 ACS on STN
AB **Insulin**-degrading enzyme (IDE) hydrolyzes **insulin** at a limited no. of sites. Although the positions of these cleavages are known, the residues of **insulin** important in its binding to IDE have not been defined. To this end, the binding of a variety of **insulin** analogs to the protease was studied in a solid-phase binding assay using immunoimmobilized IDE. Since IDE binds **insulin** with 600-fold greater affinity than it does **insulin**-like growth factor I (25 nM and .apprx.16,000 nM, resp.), the first set of analogs studied were hybrid mols. of **insulin** and IGF I. IGF I mutants [insB1-17,17-70]IGF I, [Tyr55,Gln56]IGF I, and [Phe23,Phe24,Tyr25]IGF I have been synthesized and share the property of having **insulin**-like amino acids at positions corresponding to primary sites of cleavage of **insulin** by IDE. Whereas the first 2 exhibit affinities for IDE similar to that of wild type IGF I, the [Phe23,Phe24,Tyr25]IGF I analog has a 32-fold greater affinity for the immobilized enzyme. Replacement of Phe-23 by Ser eliminates this increase. Removal of the 8 amino acid D-chain region of IGF I (which has been predicted to interfere with binding to the 23-25 region) results in a 25-fold increase in affinity for IDE, confirming the importance of residues 23-25 in the high-affinity recognition of IDE. A similar role for the corresponding (B24-26) residues of **insulin** is supported by the use of site-directed mutant and semisynthetic **insulin** analogs. **Insulin** mutants [**B25-Asp**] **insulin** and [**B25**-His]**insulin** display 16- and 20-fold decreases in IDE affinity vs. wild-type **insulin**. Similar decreases in affinity are obsd. with the C-terminal truncation mutants [B1-24-His25-NH2]**insulin** and [B1-24-Leu25-NH2] **insulin**, but not [B1-24-Trp25-NH2]**insulin** and [B1-24-Tyr25-NH2]**insulin**. The truncated analog with the lowest affinity for IDE ([B1-24-His25-NH2]**insulin**) has one of the highest affinities for the **insulin** receptor. Thus, a region of the **insulin** mol. responsible for its high-affinity interaction with IDE was identified. Although the same region has been implicated in the binding of **insulin** to its receptor, data suggest that the structural determinants required for binding to receptor and IDE differ.

RC 660 A1 D 4 (micro

L14 ANSWER 7 OF 11 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 91340787 EMBASE
DN 1991340787
TI Receptor binding and tyrosine kinase activation by **insulin** analogues with extreme affinities studied in human hepatoma HepG2 cells.
AU Drejer K.; Kruse V.; Larsen U.D.; Hougaard P.; Bjorn S.; Gammeltoft S.
CS Novo-Nordisk A/S,DK-2880 Bagsvaerd, Denmark
SO Diabetes, (1991) 40/11 (1488-1495).
ISSN: 0012-1797 CODEN: DIAEAZ
CY United States
DT Journal; Article
FS 003 Endocrinology
037 Drug Literature Index
LA English
SL English

=> d 7 hit

L14 ANSWER 7 OF 11 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
TI Receptor binding and tyrosine kinase activation by **insulin** analogues with extreme affinities studied in human hepatoma HepG2 cells.
AB The **insulin**-receptor affinity of five human **insulin** analogues with one to four amino acid substitutions was measured with human hepatoma cells (HepG2). The binding affinities ranged from 0.05% for **Asp(B25) insulin**, 18% for **Asp**(B9),Glu(B27) **insulin**, 80% for Asp(B28) **insulin**, and 327% for Asp(B10) **insulin** to 687% for His(A8),His(B4),Glu(B10),His(B27) **insulin** relative to human **insulin**. Binding constants obtained by competition experiments at steady state with [125I]Tyr(A14)-labeled **insulin** and unlabeled analogues and by kinetic studies with [125I]Tyr(A14)-labeled analogues and **insulin** gave essentially the same values. The kinetic studies showed that differences in affinity between analogues were due to differences in both dissociation and association rate constants. The affinity for **insulinlike** growth factor I receptor was low, ranging from <0.005% for **Asp(B25) insulin** to 0.6% for His(A8),His(B4),Glu(B10),His(B27) **insulin**. The potencies of **insulin** analogues in activation of the tyrosine kinase of solubilized and partially purified **insulin** receptors from HepG2 cells, measured with the exogenous substrate poly(Glu80-Tyr20), ranked in the same order as the binding affinities, the actual values being somewhat elevated for the high-affinity analogues, however. We conclude that these human **insulin** analogues are active in **insulin**-receptor binding and tyrosine kinase stimulation but show wide variation in affinity.
CT Medical Descriptors:
*hepatoma cell
*kidney
article
controlled study
human
human cell
priority journal
Drug Descriptors:
***insulin receptor**
***insulin: PD, pharmacology**
***insulin: CM, drug comparison**
***insulin derivative: PD, pharmacology**
***insulin derivative: CM, drug comparison**
*protein tyrosine kinase: EC, endogenous compound
RN (**insulin**) 9004-10-8; (protein tyrosine kinase) 80449-02-1

L14 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:491611 BIOSIS
DN PREV199799790814
TI Metabolically inactive **insulin** analog prevents type I diabetes in prediabetic NOD mice.
AU Karounos, D. G. (1); Bryson, J. S.; Cohen, D. A.
CS (1) Dep. Intern. Med., Univ. Kentucky Med. Cent., 800 Rose St., Rm. MN520, Lexington, KY 40536-0084 USA
SO Journal of Clinical Investigation, (1997) Vol. 100, No. 6, pp. 1344-1348. ISSN: 0021-9738.
DT Article
LA English

=> d 9 ab

L14 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AB The purpose of this study was to determine the relative importance of the metabolic effects of **insulin** for diabetes prevention by administering **insulin** or an inactive **insulin** analog by daily subcutaneous injections to prediabetic mice. A recombinant monomeric human **insulin** analog, which does not bind to the **insulin** receptor as a consequence of an alteration of a single amino acid at position 25 of the B chain, was shown to be equally effective at diabetes prevention as was intact **insulin**. In contrast to native **insulin**, the **insulin** analog did not cause hypoglycemia after subcutaneous injection. The **insulin** analog, however, protected young adult mice from diabetes, even when it was initiated after the onset of extensive lymphocytic infiltration of the islets. Thus, preventative therapy by daily subcutaneous injections of **insulin** does not require the hypoglycemic response, or binding to the **insulin** receptor to prevent the onset of type I diabetes.

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WEST Search History

DATE: Friday, July 25, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L13	L12 and insulin$	7	L13
L12	Worsaae	26	L12
L11	L10 and insulin$	16	L11
L10	dyrberg	29	L10
L9	L8 and insulin$	1	L9
L8	Mandic	46	L8
L7	L4 near10 (acid or acidic or hydrophilic)	17	L7
L6	L5 not l1	0	L6
L5	L4 near10 (Asp or aspart$)	2	L5
L4	(insulin$)near10(B25)	36	L4
L3	L2 not l1	0	L3
L2	(asp or aspartyl or aspartat$)near3 (B25)or Asp-B25	2	L2
L1	(insulin$) and (asp or aspartyl or aspartat$)near3 (B25)	2	L1

END OF SEARCH HISTORY